IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	RAUL, *et al.*	**Confirmation No.:**	9898
Application No.:	10/589,524	**Group Art Unit:**	1611
Filed:	August 15, 2006	**Examiner:**	Orwig, Kevin S.
Attorney No.:	DC5078 PCT1		
Title:	METHOD OF MAKING SILICONE PRESSURE SENSITIVE ADHESIVES FOR DELIVERING HYDROPHILIC DRUGS		

SUPPLEMENTAL DECLARATION UNDER 37 C.F.R. § 1.132

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Commissioner for Patents
P.O. Box 1450
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Dear Sir:

I, Gerald K. Schalau, II, hereby state that:

1. I am a citizen of the United States of America.

2. I am currently employed as an Industry Specialist for Dow Corning Corporation in Midland, MI in the Healthcare Industries Science and Technology Group. I have worked in the field of developing adhesives for transdermal drug delivery and wound care for about 8 years and have been employed with Dow Corning Corporation since 1998. I earned a Bachelor of Science degree in biology from Eastern Nazarene College in Quincy, MA in 1990 and an MBA in from Northwood University, Midland MI in 2005. I am a co-inventor of 8 U.S. patents/patent applications.

3. I am a co-inventor of the pending application, Application Serial No. 10/589,524, and a person highly skilled in the art of developing adhesives for transdermal drug delivery.

Description of Attached Supporting Figures:

4. The following Figures are attached hereto and submitted as evidence to appropriately support my statements below:

Figure 1a is a micrograph of the drug particles of niacinamide, which is a hydro*philic* drug, formed in the First Example of This Invention that is described in detail below. This micrograph clearly shows a drug particle that is much smaller than the large drug particles of Figure 1b which corresponds to the First Comparative Example.

Figure 1b is a micrograph of the drug particles formed in the First Comparative Example that is described in detail below. This micrograph clearly shows a large mass that is either a large drug particle or an agglomeration of large drug particles. In either scenario, the mass is much larger than the small drug particles of Figure 1a.

Figure 2 is a bar graph that represents the Second Example of This Invention and the Second Comparative Example. The Second Example of This Invention demonstrates controlled and less variable drug release of niacinamide, both in terms of a total weight release and standard deviation, from the smaller drug particles of Figure 1a. These results are compared to results from the Second Comparative Example wherein total weight release and standard deviation of the larger particles of Figure 1b are less controlled and more variable.

General Description of Problems with the Prior Art and with Related Technology:

5. Hydrophilic drugs and/or hydrophilic excipients are not readily soluble or compatible in hydrophobic matrices of silicone pressure sensitive adhesives. For example, when hydrophilic drugs/excipients are combined with hydrophobic silicone pressure sensitive adhesives, the drugs/excipients tend to cake and/or large crystals and/or agglomerates of the drugs/excipients form due to non-homogenous distribution and mixing. Said differently, the

hydrophilic drugs/excipients do not evenly distribute in the hydrophobic silicone pressure sensitive adhesives due to their inherent incompatibility. This typically occurs due to hydrogen bonding, dipole-dipole interactions, and differences in polarity of the hydrophilic drugs/excipients and the hydrophobic silicone pressure sensitive adhesives.

Non-homogenous mixing, large crystal formation, caking and agglomeration are undesirable and results in formation of adhesive matrices that include low and/or inconsistent amounts of the hydrophilic drugs that can be released. This can be especially problematic in use because many drugs are designed to be released at particular rates (e.g. weight of drug released / unit time) and for predictable total lengths of time. If the adhesive matrices include low and/or inconsistent and uncontrolled levels of the hydrophilic drugs that can be released, then the drugs will not be released at the appropriate rate and/or for the appropriate total length of time. This typically results in ineffective drug treatment due to a drug release rate that is too slow or too low or in a large and sudden drug release which is also problematic.

General Description of the Superior/Unexpected Results Achieved By This Invention:

6. This invention surprisingly and unexpectedly improves upon the problems described above and includes a method of making an improved adhesive matrix. More specifically, the method of this invention promotes improved physical stability of adhesive matrices and improved predictability, control, and precision of drug release therefrom. The claimed surfactant (e.g. silicone polyether) contributes to improved tack-adhesion properties of transdermal patches that include the adhesive matrices. The surfactant/silicone polyether also contributes to more effective dispersion of solid powdered hydrophilic drugs and hydrophilic excipients thereby minimizing agglomeration and crystal formation and increasing homogenous distribution. As a whole, the method of this invention forms an adhesive matrix that releases the

hydrophilic drugs more predictably, more controllably, more precisely, and with less variance.

The Specific Order of the Method Steps of This Invention:

7. The method of this invention includes a series of ***sequential*** steps set forth in both claims 1 and 12 which produce the superior and unexpected results of this invention.

(1) The first step involves forming the semi-solid composition containing the solid powdered hydrophilic drug or the solid powdered hydrophilic excipient and the surfactant (e.g. a silicone polyether). Said differently, the surfactant and the drug/excipient are combined with each other independently from any other method steps and apart from the adhesive.

(2) The second step involves combining the adhesive (e.g. a silicone pressure sensitive adhesive), or a solution containing a solvent and the adhesive, and the semi-solid composition formed in (1) the first step.

(3) The third step involves mixing the semi-solid composition and the adhesive or the solution containing the solvent and the adhesive to form the adhesive matrix.

As shown in the attached Figures and explained in greater detail below, the claimed order of the method steps produces superior and unexpected results. More specifically, this order of method steps (i) results in formation of smaller hydrophilic drug particles in the adhesive matrices and (ii) minimizes agglomeration and crystal formation of the hydrophilic drugs which (iii) promote more predictable, more well-controlled, more precise, and less variable drug release from the adhesive matrices.

Experimental Data Supporting Superior and Unexpected Results – Particle Size:

8. The following experiments demonstrate that size of drug particles is surprisingly and unexpectedly affected by the sequential order of the method steps of this invention:

First Example of This Invention – Particle Size

In a First Example of This Invention, 10 wt% niacinamide (which is a hydrophilic drug typically available as a micronized powder) is first added to a silicone polyether that is commercially available from Dow Corning Corporation under the trade name of DC 193 Fluid. The niacinamide and silicone polyether are mixed into a paste using a mortar and pestle. This step corresponds with (1) the first claimed method step outlined above.

Subsequently, the paste is added to a silicone pressure sensitive adhesive (PSA) that is commercially available from Dow Corning Corporation under the trade name of BIO-PSA 7-4202. This PSA includes a mixture of 60% solids in 40% ethyl acetate solvent. This step corresponds with (2) the second claimed method step outlined above.

The paste and the PSA are then mixed for 90 seconds at a 100 setting on a Variac and malt-type mixer. This step corresponds with (3) the third claimed method step outlined above.

The resulting mixture is then immediately applied to a fluoropolymer release liner to devolatilize the ethyl acetate at 22°C and form an adhesive matrix.

After formation, the adhesive matrix is analyzed to determine the size of the particles of niacinamide dispersed therein, whether any agglomeration of the particles occurred, and whether any crystals formed. More specifically, the adhesive matrix is magnified 200x using a light microscope to produce a micrograph, as set forth in Figure 1a. This micrograph clearly shows a drug particle that is much smaller than the large drug particles of the First Comparative Example described immediately below.

Accordingly, this First Example, and the corresponding Figure 1a, unmistakably demonstrate that the claimed order of method steps produces superior and unexpected results

related to the production of small drug particles, especially in comparison to the First Comparative Example.

First Comparative Example – Particle Size

In a First Comparative Example, 10 wt% niacinamide is added to the PSA described above (7-4202). Notably, this first step is very different from (1) the first claimed method step of this invention outlined above.

Subsequently, the mixture of the niacinamide and the PSA is added to the silicone polyether described above (DC 193 Fluid). This second step is also very different from (2) the second claimed method step outlined above.

Then, the mixture of the niacinamide, the PSA, and the silicone polyether is stirred for 90 seconds at a 100 setting on a Variac and malt-type mixer.

The resulting mixture is immediately applied to the fluoropolymer release liner to devolatilize the ethyl acetate at 22°C and form a comparative adhesive matrix.

After formation, the comparative adhesive matrix is also analyzed to determine the size of the particles of niacinamide dispersed therein, whether any agglomeration of the particles occurred, and whether any crystals formed. More specifically, the comparative adhesive matrix is magnified 200x using a light microscope to produce a micrograph, as set forth in Figure 1b. This micrograph clearly shows a large mass that is either a large drug particle or an agglomeration of large drug particles. In either scenario, the mass is much larger than the small drug particles of Figure 1a. Said differently, in either scenario, this First Comparative Example does not produce small drug particles which can effectively dispersed in adhesive matrices. Thus, this First Comparative Example does not promote predictable, well-controlled, precise, or less variable drug release.

<u>Size of Drug Particles – Why Smaller is More Desirable and Unexpected:</u>

<u>Smaller Drug Particles are More Desirable:</u>

9. As is well known in the art, small drug particles are desirable because they dissolve more rapidly and more predictably thereby making drug release more predictable, more well-controlled, more precise, and less variable. Conversely, large particles can dissolve slowly and ineffectively thereby causing too low of a dose of the drug to be released at any one time or over a particular length of time. This is clearly undesirable because the drug may not be effective at the low dose. Alternatively, large particles can dissolve all at once thereby causing a great excess (e.g. a "spike") of the drug to be released. This is also very undesirable due to potentially harmful effects that could result. Moreover, crystal formation is also undesirable. Crystals are not readily bio-available and thus can also cause too low of a dose of the drug to be released at any one time or over a particular length of time or prevent release of the drug altogether.

The size of the niacinamide drug particles shown in Figure 1b are significantly larger than those shown in Figure 1a. Accordingly, the small drug particles of this invention are desirable and contribute to more predictable, well-controlled, more precise, and less variable drug release.

<u>Small Drug Particles are Unexpected:</u>

10. The small size of the drug particles formed using this invention is unexpected for multiple reasons.

As related to the First Comparative Example described above, it is expected that the hydrophilic drug (i.e., niacinamide) would disperse more effectively, quickly, and completely when added to a mixture of the PSA and the silicone polyether because the PSA includes 40 wt%

of solvent. Thus, it would be expected that the First Comparative Example would produce very small drug particles. However, this is not the case. In fact, just the opposite is true. As seen in the First Example of This Invention, the hydrophilic drug *surprisingly* disperses more effectively and completely when added to the silicone polyether first, especially given that there is no solvent in the silicone polyether. This more effective and complete dispersion produces the smaller drug particles.

As also related to the First Comparative Example described above, it is expected that the mixture of the PSA and the silicone polyether would more efficiently coat the drug particles due to the hydrophilicity of the drug and the corresponding polarity of the mixture of the PSA and the silicone polyether. It is also expected that the entire matrix of the PSA would be made more hydrophilic through addition of the silicone polyether thereby improving the probability of the hydrophilic drug being more adequately dispersed throughout the entire matrix. Thus, it is expected that more efficient coating would reduce agglomeration and caking of the drug particles. However, this is again not the case and just the opposite is true. As seen in the First Example of This Invention, the hydrophilic drug *surprisingly* resists caking and agglomeration (seen relative to the smaller particle size) as compared to the First Comparative Example. This is likely due to the unexpected and more efficient coating of the drug particles resulting from use of the method of this invention.

Experimental Data Supporting Superior and Unexpected Results – Drug Release:

11. The following experiments demonstrate that the size of the drug particles that are formed from the instant method positively affects the precision of the drug release:

Second Example of This Invention - Predictable and Less Variable Drug Release

In a Second Example of This Invention, three 1.9 cm diameter discs are cut from the adhesive matrix of the First Example of This Invention described above. A weight percent of niacinamide released from these discs is then determined using a Franz cell with a 0.9% sodium chloride solution in water as a receptor fluid, using a procedure well known in the art. The weight percent of niacinamide released at 1, 2, 4, 6 and 8 hour intervals is measured using HPLC. The results of these determinations are set forth in Figure 2 and represented by the bars labeled with double asterisks (**).

Second Comparative Example – Less Predictable and More Variable Drug Release

In a Second Comparative Example, three 1.9 cm diameter discs are cut from the adhesive matrix of the First Comparative Example described above. A weight percent of niacinamide released from these discs is then determined using a Franz cell with a 0.9% sodium chloride solution in water as a receptor fluid, using a procedure well known in the art. The weight percent of niacinamide released at 1, 2, 4, 6 and 8 hour intervals is measured using HPLC. The results of these determinations are set forth in Figure 2 and represented by the bars labeled with a single asterisk (*).

Why More Predictable and Less Variable Drug Release is Desirable and Unexpected:

More Predictable and Less Variable Drug Release is Desirable:

It is well known in the art that the predictable release of a particular weight or amount of a drug is very important to achieve desired results. Typically, particular weight amounts of drugs must be released in order for the drugs to be effective and yet not toxic. However, the variability of the release of the drug may be even more important than the weight of the drug released to ensure proper dosing and treatment using the drug.

In Figure 2, even if the error bars of the First Example of This Invention overlap with those of the First Comparative Example, the errors bars associated with this invention are much smaller relative to the mean (i.e., height of the error bar). The size of the error bars, even more so than any overlap, indicates that the method of this invention reduces variability in drug release. As described in detail above, more predictable, well-controlled, more precise, and less variable drug release is highly desirable.

More Predictable and Less Variable Drug Release is Unexpected:

The more predictable, well-controlled, precise, and less variable drug release shown in the data and associated with the method of this invention is unexpected for many of the same reasons as described above. The hydrophilic drug *surprisingly* disperses more effectively and completely when added to the silicone polyether first, thereby unexpectedly producing the smaller drug particles. Thus, the corresponding improved drug release is also surprising and unexpected.

Moreover, it is expected that adding the hydrophilic drug to the mixture of the PSA and the silicone polyether in the Comparative Examples would result in improved dispersion of the drug in the adhesive matrix thereby yielding smaller drug particles and more predictable and well-controlled drug release. Yet again this is not the case and the opposite remains true. As seen in both the First and Second Examples of This Invention described above, the method of this invention surprisingly and unexpectedly forms smaller drug particles than the Comparative Example which results in more predictable, well-controlled, more precise, and less variable drug release.

12. In conclusion, it is very clear from my perspective of one of high skill in the art of developing adhesives for transdermal drug delivery that the instant method produces surprising

and unexpected results. The sequential steps of the method produce smaller drug particles than in the Comparative Examples which corresponds to more predictable, more well-controlled, more precise, and less variable drug release.

13. I hereby declare that all statements made herein of my own knowledge are true, that all statements made on information described herein are believed to be true, that all data described herein in the attached Exhibits are true, and further that these statements and data are made and presented with the knowledge that willful and false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or patent issued thereon.

Respectfully submitted,

Dated 04 Mar 16

Gerald K. Schalau, II

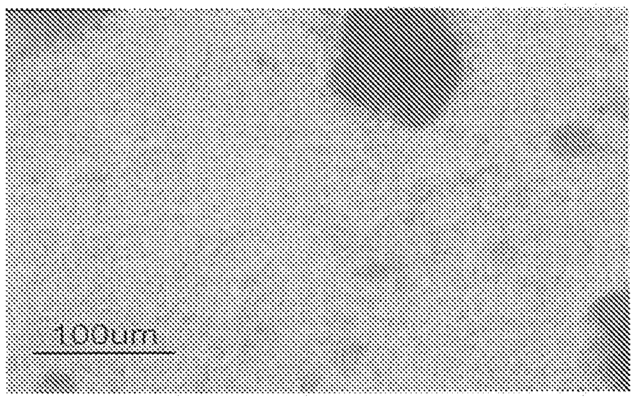

Figure 1a

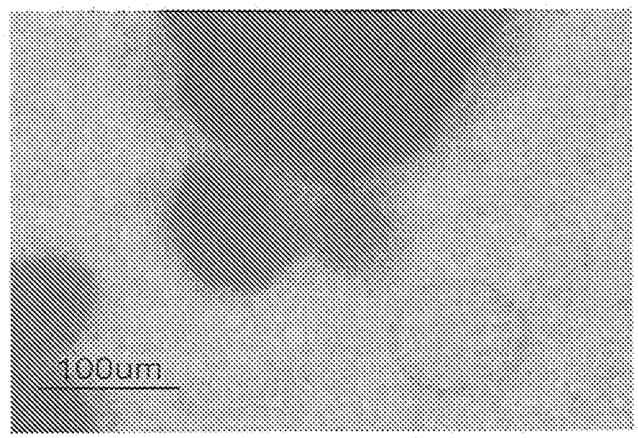

Figure 1b

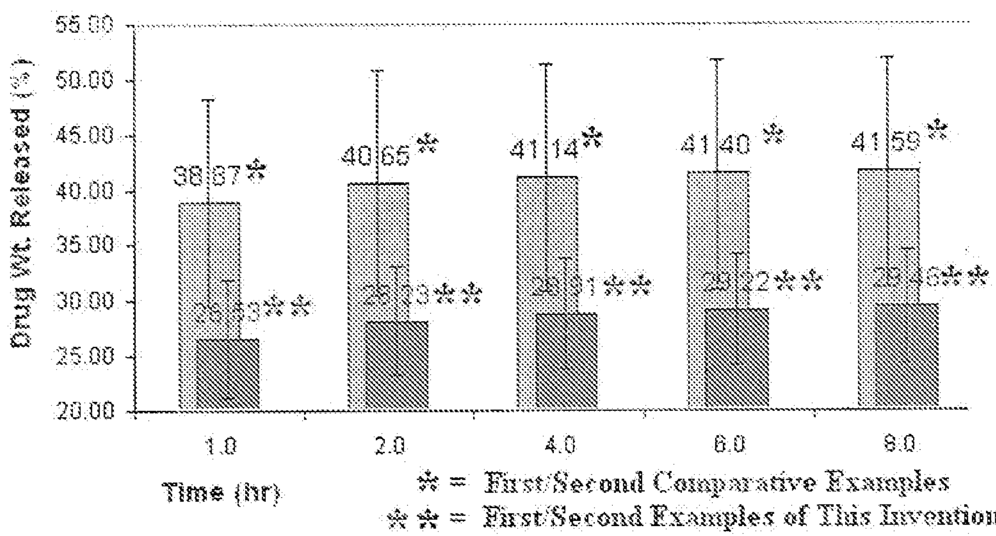

Figure 2